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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STITZEL, DAVID PAUL	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,801	GATTI, PAOLO	
	Examiner	Art Unit	
	David P. Stitzel, Esq.	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,8-16,18-43,45-56,59,61-77,79-85,87 and 92* is/are pending in the application.

4a) Of the above claim(s) *3 and 5-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,8-16,18-43,45-56,59,61-77,79-85,87 and 92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/11/04; 6/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

OFFICIAL ACTION

Acknowledgment of Receipt

Receipt of the Applicant's Response and Election, which was filed on January 4, 2006, of the following: 1. *the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide* as the single specific patentably distinct species of the *indolinone molecule of formula (I)*, as recited in generic claims 1, 72-76, and 92; 2. *mannitol* as the single specific patentably distinct species of *diluent*, as recited in generic claim 8; 3. *polyvinylpyrrolidone* as the single specific patentably distinct species of *binder*, as recited in generic claim 9; 4. *croscarmellose sodium* as the single specific patentably distinct species of *disintegrant*, as recited in generic claim 10; and 5. *magnesium stearate* as the single specific patentably distinct species of *lubricant*, as recited in generic claim 11; to the Official Action dated September 9, 2005, is acknowledged. However, Applicant failed to provide a qualifying statement as to whether the aforementioned election was "with traverse" or "without traverse." Therefore, since the Applicant did not distinctly and specifically point out any alleged errors in the Examiner's restriction requirement, the election has been treated as an election *without traverse*, pursuant to MPEP § 818.03(a).

Status of Claims

Claims 12-16, 18-24 and 76 were amended, and claims 17, 44, 57, 58, 60, 78, 86, 88-91 and 93-106 were canceled, by an amendment that accompanied the aforementioned Response. In addition, claims 3 and 5-7 are withdrawn from further consideration as being directed to a non-elected invention. As a result, claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77, 79-85, 87 and 92 are currently pending and therefore examined herein on the merits for patentability.

Claim Rejections - 35 U.S.C. § 102

The following are quotations of the appropriate paragraphs of 35 U.S.C. § 102, which form the basis of the anticipation rejections as set forth under this particular section of the Official Action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77 and 92 are rejected under 35 U.S.C. § 102(b) as being anticipated by International Application Publication WO01/37820 (hereinafter the Shenoy '820 publication).

With respect to claims 1, 2, 4, 12-16, 18-24, 72-77 and 92 of the instant application, the Shenoy '820 publication discloses a solid formulation comprising a malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide present in an amount from about 0.01 % by weight to about 90 % by weight, as recited in claims 1, 2, 4, 12-16, 18-24, 72-77 and 92 of the instant application (page 14, lines 4-5; page 39, compound 80; page 60, lines 1-8; page 64, lines 9-11; page 65, lines 1-4; page 72, lines 18-31; page 76, lines 1-3; page 82, lines 24-25; page 92, lines 8-30; page 93, lines 1-4; page 96, lines 5-29; page 158, lines 28-30; page 159, lines 1-8; and claim 11).

With respect to claims 8-11, 25-43, 45-56, 59 and 61-71 of the instant application, the Shenoy '820 publication discloses that said solid formulation further comprises: mannitol as a diluent, which is present in an amount from about 10 % by weight to about 80 % by weight, as recited in claims 8, 25-37 and 68; polyvinylpyrrolidone as a binder, which is present in an amount from about 2 % by weight to about 20 % by weight, as recited in claims 9, 38-43, 45-48 and 69; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose) as a disintegrant, which is present in an amount from about 2 % by weight to about 20 % by weight, as recited in claims 10, 49-56 and 70; and magnesium stearate as a lubricant, which is present in an amount from about 1 % by weight to about 2 % by weight, as recited in claims 11, 61-67 and 71 (page 61, lines 14-28; page 73, lines 1-31; page 82, lines 28-30; page 84, lines 8-9, 12-13 and 26; page 93, lines 1-4; page 96, lines 5-29; page 233, lines 6-10; claims 50, 52-54 and 56).

2. Claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77, 79, 80, 83-85, 87 and 92 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pre-Grant Patent Application Publication 2003/0130280 (hereinafter the O'Farrell '280 publication).

With respect to claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77, 79, 80, 83-85, 87 and 92 of the instant application, the O'Farrell '280 publication discloses a solid formulation comprising an L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide present in an amount from about 40.0 % by weight to about 75.0 % by weight, as recited in claims 1, 2, 4, 12-16, 18-24, 72-77, 79, 80, 83-85, 87 and 92 of the instant application ([0044]-[0046], [0048], [0107], [0160], [0166]-[0167], [0203]-[0205]; claim 13); wherein said solid formulation further comprises: mannitol, which is present in an amount from

about 13.5 % by weight to about 47.5 % by weight, as recited in claims 8, 25-37, 68, 79, 80, 83-85 and 87 of the instant application; polyvinylpyrrolidone, which is present in an amount of about 5 % by weight, as recited in claims 9, 38-43, 45-48, 69, 79, 80, 83-85 and 87 of the instant application; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose), which is present in an amount of about 6 % by weight, as recited in claims 10, 49-56, 70, 79, 80, 83-85 and 87 of the instant application; and magnesium stearate, which is present in an amount from about 0.5 % by weight to about 1.5 % by weight, as recited in claims 11, 61-67, 71, 79, 80, 83-85 and 87 of the instant application ([0164]-[0165], [0180], [0186], [0188]-[0190], [0203]-[0205]).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 103, which forms the basis of the obviousness rejections as set forth under this particular section of the Official Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 79-85 and 87 are rejected under 35 U.S.C. § 103(a) as being unpatentable over International Application Publication WO01/37820 (hereinafter the Shenoy '820 publication).

The teachings of the Shenoy '820 publication are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove.

With respect to claims 79-85 and 87 of the instant application, although the Shenoy '820 publication teaches a solid formulation comprising a malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide

present in an amount from about 0.01 % by weight to about 90 % by weight; wherein said solid formulation further comprises: mannitol as a diluent, which is present in an amount from about 10 % by weight to about 80 % by weight; polyvinylpyrrolidone as a binder, which is present in an amount from about 2 % by weight to about 20 % by weight; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose) as a disintegrant, which is present in an amount from about 2 % by weight to about 20 % by weight; and magnesium stearate as a lubricant, which is present in an amount from about 1 % by weight to about 2 % by weight; the Shenoy '820 publication fails to explicitly teach the specific embodiments of the solid formulations recited in claims 79-85 and 87 of the instant application.

However, while the Shenoy '820 publication patent does not explicitly teach the specific embodiments of the solid formulations recited in claims 79-85 and 87 of the instant application, it is well within the purview of the skilled artesian to determine the optimal weight percent range of each ingredient therein by systematically adjusting the concentrations thereof during the course of routine experimentation. With a particular emphasis on page 73, lines 1-31; page 93, lines 1-4; page 96, lines 5-29; and claims 50, 52-54 and 56 of the Shenoy '820 publication, one of ordinary skill in the art at the time the instant application was filed would have been motivated to systematically adjust the concentrations of each ingredient, during the course of routine experimentation, so as to obtain pharmaceutically effective solid formulations as claimed in claims 79-85 and 87 of the instant application. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 105 USPQ 233, 235 (CCPA 1955). "The normal desire of scientists or artisans to improve upon what is already

generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." See *Peterson*, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003).

2. Claims 81 and 82 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pre-Grant Patent Application Publication 2003/0130280 (hereinafter the O'Farrell '280 publication).

The teachings of the O'Farrell '280 publication are incorporated herein by reference and are therefore applied in the instant rejection as discussed hereinabove.

With respect to claims 81 and 82 of the instant application, although the O'Farrell '280 publication teaches a solid formulation comprising an L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide present in an amount from about 40.0 % by weight to about 75.0 % by weight; wherein said solid formulation further comprises: mannitol, which is present in an amount from about 13.5 % by weight to about 47.5 % by weight; polyvinylpyrrolidone, which is present in an amount of about 5 % by weight; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose), which is present in an amount of about 6 % by weight; and magnesium stearate, which is present in an amount from about 0.5 % by weight to about 1.5 % by weight; the O'Farrell '280 publication fails to explicitly teach the specific embodiments of the solid formulations recited in claims 81 and 82 of the instant application.

However, while the O'Farrell '280 publication patent does not explicitly teach the specific embodiments of the solid formulations recited in claims 81 and 82 of the instant application, it is well within the purview of the skilled artesian to determine the optimal weight percent range of each ingredient therein by systematically adjusting the concentrations thereof during the course of routine

experimentation. One of ordinary skill in the art at the time the instant application was filed would have been motivated to systematically adjust the concentrations of each ingredient, during the course of routine experimentation, so as to obtain pharmaceutically effective solid formulations as claimed in claims 81 and 82 of the instant application. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See *In re Aller*, 105 USPQ 233, 235 (CCPA 1955). "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." See *Peterson*, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003).

3. Claims 1, 2, 4, 8-11, 68-77 and 92 are rejected under 35 U.S.C. § 103(a) as being unpatentable International Application Publication WO01/45689 (hereinafter the Lipson '689 publication).

With respect to claims 1, 2, 4, 8-11, 68-77 and 92 of the instant application, the Lipson '689 publication teaches a solid formulation comprising: a malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide; wherein said solid formulation may further comprise: mannitol; polyvinylpyrrolidone; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose); and magnesium stearate (page 16, lines 13-15, compound 16; page 17, lines 16-18; page 34, lines 12-15; page 35, lines 13-14, 20 and 22-24; page 36, lines 4-5; page 38, lines 13-15; claim 10, page 56, compound XVIX). However, the Lipson '689 publication does not explicitly teach the specific weight percent of the malate salt of said 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide active ingredient within the solid formulation, as claimed in claims 1 and 92

of the instant application. It would have been prima facie obvious to one of ordinary skill in the art at the time the instant application was filed to determine a therapeutically effective amount of the active ingredient within the solid formulation. Determination of a therapeutically effective amount of the active ingredient within the solid formulation is well within the capability of those of ordinary skill in the art at the time the instant application was filed, especially in light of the detailed disclosure within the Lipson '689 publication (page 9, lines 21-25; page 38, lines 17-30; page 39, lines 1-30). One of ordinary skill in the art at the time the instant application was filed would have been motivated to determine, during the course of routine experimentation, the therapeutically effective amount of the active ingredient within the solid formulation so as to prevent, alleviate and/or ameliorate disease symptoms and prolong the survival of a patient being treated.

4. Claims 1, 2, 4, 8-11, 68-77 and 92 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pre-Grant Patent Application Publication 2003/0069298 (hereinafter the Hawley '298 publication).

With respect to claims 1, 2, 4, 8-11, 68-77 and 92 of the instant application, the Hawley '298 publication discloses a solid formulation comprising: an L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide; wherein said solid formulation may further comprise: mannitol; polyvinylpyrrolidone; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose); and magnesium stearate ([0006], [0007], [0027], [0067]-[0069], claims 1 and 2). However, the Hawley '298 publication does not explicitly teach the specific weight percent of the malate salt of said 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-

diethylaminoethyl)amide active ingredient within the solid formulation, as claimed in claims 1 and 92 of the instant application. It would have been prima facie obvious to one of ordinary skill in the art at the time the instant application was filed to determine a therapeutically effective amount of the active ingredient within the solid formulation. Determination of a therapeutically effective amount of the active ingredient within the solid formulation is well within the capability of those of ordinary skill in the art at the time the instant application was filed ([0083]-[0087]). One of ordinary skill in the art at the time the instant application was filed would have been motivated to determine, during the course of routine experimentation, the therapeutically effective amount of the active ingredient within the solid formulation so as to prevent, alleviate and/or ameliorate disease symptoms and prolong the survival of a patient being treated.

5. Claims 1, 2, 4, 8-11, 68-77 and 92 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pre-Grant Patent Application Publication 2002/0156292 (hereinafter the Tang '292 publication).

With respect to claims 1, 2, 4, 8-11, 68-77 and 92 of the instant application, the Tang '292 publication discloses a solid formulation comprising: an L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide; wherein said solid formulation may further comprise: mannitol; polyvinylpyrrolidone; croscarmellose sodium (a.k.a., crosslinked sodium carboxymethylcellulose); and magnesium stearate ([0149], [0153]-[0156], page 39, structure 80, [0318]-[0319], [0326]-[0329], claim 49). However, the Tang '292 publication does not explicitly teach the specific weight percent of the malate salt of said 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide active ingredient within the solid formulation, as claimed

in claims 1 and 92 of the instant application. It would have been prima facie obvious to one of ordinary skill in the art at the time the instant application was filed to determine a therapeutically effective amount of the active ingredient within the solid formulation. Determination of a therapeutically effective amount of the active ingredient within the solid formulation is well within the capability of those of ordinary skill in the art at the time the instant application was filed ([0342]-[0349]). One of ordinary skill in the art at the time the instant application was filed would have been motivated to determine, during the course of routine experimentation, the therapeutically effective amount of the active ingredient within the solid formulation so as to prevent, alleviate and/or ameliorate disease symptoms and prolong the survival of a patient being treated.

Conclusion

Claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77, 79-85, 87 and 92 are rejected because the claimed invention would have been anticipated and/or prima facie obvious to one of ordinary skill in the art at the time the invention was made since each and every element of the claimed invention, as a whole, is disclosed in and/or would have been reasonably suggested by the teachings of the cited prior art references.

Contact Information

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to David P. Stitzel, Esq. whose telephone number is 571-272-8508. The Examiner can normally be reached on Monday-Friday, from 7:30AM-6:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Sreenivasan Padmanabhan can be reached at 571-272-0629. The central fax number for the USPTO is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published patent applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished patent applications is only available through Private PAIR. For more information about the PAIR system, please see http://pair-direct.uspto.gov. Should you have questions about acquiring access to the Private PAIR system, please contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David P. Stitzel, Esq.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER